The impact of endovascular lower-limb revascularisation on the aortic augmentation index in patients with peripheral arterial disease

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Abstract: OBJECTIVES: The aortic augmentation index (AIx), a marker of arterial stiffness, and peripheral arterial disease (PAD) are associated with an increased cardiovascular risk. In claudicants, the effect of balloon angioplasty (percutaneous transluminal angioplasty, PTA) on AIx has not been determined so far. METHODS: Measurements of the ankle-brachial pressure index (ABI) and AIx were performed before and 3 months after PTA and compared to age- and sex-matched PAD patients under best medical treatment. RESULTS: The data of 61 patients (44% female, mean age 68 years) who underwent lower-limb PTA was compared to 48 conservatively treated patients (38% female, mean age 68 years). ABI significantly improved after PTA from 0.73 ± 0.02 to 0.85 ± 0.03 (p = 0.001), but remained unchanged in the control group (0.85 ± 0.23 and 0.80 ± 0.21; p = 0.16). Revascularisation was associated with a significant reduction of AIx from 31.5 ± 1.1% to 28.8 ± 1.1% after 3 months (p = 0.01). In the conservatively treated group, AIx did not change during follow-up (29.9 ± 1.1% to 29.9 ± 1.1%; p = 0.83). CONCLUSION: Lower-limb revascularisation in PAD Rutherford stage II-III is associated with an improvement of markers for arterial stiffness.

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The Impact of Endovascular Lower-limb Revascularisation on the Aortic Augmentation Index in Patients with Peripheral Arterial Disease

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WHAT THIS PAPER ADDS

The aortic augmentation index is a surrogate marker for arterial stiffness and cardiovascular mortality. This study shows for the first time that an endovascular revascularisation in claudicants is associated with an improvement of this marker, indicating beneficial systemic vascular effects beyond the improvement in perfusion of the treated leg.

Objectives: The aortic augmentation index (AIx), a marker of arterial stiffness, and peripheral arterial disease (PAD) are associated with an increased cardiovascular risk. In claudicants, the effect of balloon angioplasty (percutaneous transluminal angioplasty, PTA) on AIx has not been determined so far.

Methods: Measurements of the ankle–brachial pressure index (ABI) and AIx were performed before and 3 months after PTA and compared to age- and sex-matched PAD patients under best medical treatment.

Results: The data of 61 patients (44% female, mean age 68 years) who underwent lower-limb PTA was compared to 48 conservatively treated patients (38% female, mean age 68 years). ABI significantly improved after PTA from 0.73 ± 0.02 to 0.85 ± 0.03 ($p = 0.001$), but remained unchanged in the control group (0.85 ± 0.23 and 0.80 ± 0.21; $p = 0.16$). Revascularisation was associated with a significant reduction of AIx from 31.5 ± 1.1% to 28.8 ± 1.1% after 3 months ($p = 0.01$). In the conservatively treated group, AIx did not change during follow-up (29.9 ± 1.1% to 29.9 ± 1.1%; $p = 0.83$).

Conclusion: Lower-limb revascularisation in PAD Rutherford stage II–III is associated with an improvement of markers for arterial stiffness.

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Keywords: Peripheral arterial disease, Aortic augmentation index, Lower-limb revascularisation

Peripheral arterial disease (PAD) affects more than 20% of the elderly population and is associated with an increased risk for cardiovascular events such as myocardial infarction and stroke.[1–6] The severity of PAD is a marker for the atherosclerotic burden in other vascular beds, and a correlation between the ankle–brachial arterial pressure index (ABI) and mortality has been reported.[3] Patients with critical limb ischaemia have the lowest survival rate with an annual cardiovascular mortality rate of 25%.[7] Patients with claudication or even asymptomatic PAD have a five- to 10-fold greater risk of myocardial infarction and stroke than a control population.[1]

Despite this astonishing epidemiologic data, the mechanisms through which PAD is associated with this increased risk are still not fully understood. So far, possible explanations are increased markers of inflammation and oxidative stress that eventually impact acute vascular events.[8] In addition, reduced ambulatory activity due to claudication is closely associated with cardiovascular morbidity and mortality in patients with atherosclerotic disease.[9–11] Furthermore, altered arterial-wall properties, such as arterial stiffness, might be another mechanism due to which patients with PAD had an increased cardiovascular risk. The augmentation index (AIx), derived from the aortic-pressure waveform acquired by applanation tonometry, is a surrogate marker of arterial stiffness and correlates with cardiovascular mortality.[12–14]

Several authors have already demonstrated an association between ABI and AIx.[15–17]

So far, the effect of lower-limb revascularisation in patients with PAD on AIx has not been studied. Since endovascular procedures improve ABI, we hypothesise that lower-limb revascularisation may improve AIx in claudicants.

METHODS

Study design and patients

The study was conducted at a tertiary referral centre as a prospective, non-randomised, single-centre, controlled

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study. The local ethics committee approved the study and all patients gave written informed consent.

Patients with stable PAD Rutherford stage II—III of at least for 6 months without improvement during non-supervised walking exercise and substantial limitation in their walking capacity affecting their quality of life underwent endovascular revascularisation (group A). Patients with Rutherford stage I—II who did not feel substantially limited in their daily life received best medical treatment and without revascularisation (group B). Exclusion criteria were critical limb ischaemia (Rutherford IV—VI), cardiac arrhythmia, chronic inflammatory vascular disorders or failed revascularisation defined as more than 50% residual stenosis confirmed angiographically or by duplex ultrasound after the procedure. Patients were graded in Rutherford stages by medical history.

The following data were collected at baseline and after 3 months: medical history, cardiovascular risk factors, co-morbidities, medication, systolic and diastolic blood pressure, body mass index, ABI and radial artery pulse-wave analysis. At the follow-up, a duplex scan was performed if indicated based on clinical and vascular examinations.

Ankle—brachial arterial pressure index and radial artery pulse-wave analysis

The ankle—brachial arterial pressure index (ABI) was assessed with the patient in the supine position. Systolic ankle blood pressure of the posterior and anterior tibial artery and of the peroneal artery in both legs was obtained with a hand-held 6-MHz Doppler probe (Kranzbühler, Logidop 2, Pilger Medical Electronics, Switzerland). The ABI was calculated for each leg as the ratio of the highest systolic blood pressure in the ankle divided by the highest brachial systolic blood pressure. The ABI of the limiting leg was taken as the study parameter.

AIx was derived via a waveform measured at the radial artery using the SphygmoCor system (AtCor Medical; Sydney, Australia) as previously described;[18] this measurement was performed by a single investigator with patients in the supine position. The aortic-pressure waveform was derived from the radial waveform recorded using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Houston, TX, USA) and a previously validated generalised transfer function.[19,20] Aortic augmentation pressure was calculated as the difference between the first and the second systolic peaks of the ascending aortic waveform, and AIx was expressed as a percentage of pulse pressure (the difference between central systolic and diastolic pressure). Because AIx is influenced by heart rate, an index normalised for a heart rate of 75 bpm was used, in accordance with Wilkinson et al.[21]

Medical treatment and endovascular procedure

All patients were treated according to guidelines with antiplatelet and/or anticoagulation, statins and antihypertensive therapy if indicated.

In addition to best medical treatment, patients in the percutaneous transluminal angioplasty (PTA) group (A) were treated with standard balloon angioplasty in the standard manner using a 4F—6F sheath introduced into the femoral common artery. Stent implantation was additionally performed at the discretion of the interventionist. At the beginning of the procedure, all patients received 5000 IU heparin i.a. Medication remained unchanged except for clopidogrel given over a period of 28 days in the case of stent implantation.

Statistical analysis

Data are expressed as mean ± standard error with range in parenthesis. Data were analysed with StatView 5.0.1. software (Adept Scientific, Acton, MA, USA), using the Mann—Whitney-*U* test or Fisher's exact test for intergroup comparison and the Wilcoxon signed-rank test for intra-group comparison. Values of two-sided $p < 0.05$ were considered statistically significant.

RESULTS

The effect of PTA on AIx and ABI was assessed in 61 patients (group A: 44% female, mean age 68.7 years) and compared to 48 conservatively treated patients (group B: 38% female, mean age 68.4 years). There were no failed angioplasties.

The baseline characteristics of the patients did not differ between the two groups (Table 1), except for ABI, which was lower in group A (0.72 ± 0.02) than in group B (0.84 ± 0.23; $p = 0.01$), heart rate, which was higher in group A (71.2 ± 1.3) than in group B (65.7 ± 1.1) and mean arterial pressure, which was slightly lower in the intervention group (101.3 ± 2 vs. 106.1 ± 1.8) as reported in Table 3.

Lesions characteristics of the revascularised patients are summarised in Table 2.

In the PTA group, 69% ($n = 42$) had Rutherford III and 31% ($n = 19$) Rutherford II, whereas in the control group all patients were Rutherford I—II. After 3 months, ABI had improved from 0.73 ± 0.02 to 0.85 ± 0.03 ($p = 0.001$) in group A, but remained unchanged in the conservatively treated group (0.80 ± 0.21). At 3-months follow-up, there was no significant difference in ABI between the two groups (Fig. 1).

At follow-up, no difference between the PTA and the conservatively treated group for peripheral and central pressure values had been found (Table 4).

In group A, revascularisation was associated with a significant reduction of AIx from 31.5 ± 1.1% to 28.8 ± 1.1% after 3 months ($p = 0.01$). In contrast, there was no change in AIx (29.9 ± 1.1% to 29.9 ± 1.1%; $p = 0.83$) in the conservatively treated group between baseline and follow-up (Fig. 2).

Antihypertensive medication remained unchanged and there were no significant differences between the two study groups between baseline and follow-up.

DISCUSSION

Our study shows that endovascular therapy lowers AIx, a surrogate marker for arterial stiffness. This indicates that peripheral revascularisation has a beneficial impact on pulse-wave function when compared to a control group

Table 1. Baseline characteristics of the study population.

	PTA ($n = 61$)	Control ($n = 48$)	p
BMI (kg/m^2)	25.2 (0.5)	25.5 (0.6)	0.42
Female (%)	27 (44)	16 (33)	0.32
Age (years)	68.7 (1.2)	68.4 (1.7)	0.89
ABI	0.72 (0.02)	0.84 (0.23)	0.01
Cardiovascular risk factors, *n* (%)			
Hypertension	52 (85)	38 (79)	0.45
Ever smokers	49 (80)	35 (73)	0.37
Diabetes	18 (29)	13 (27)	0.83
Dyslipidemia	42 (69)	29 (60)	0.42
Comorbidities, *n* (%)			
Coronary artery disease	18 (29)	11 (23)	0.51
Cerebrovascular disease	19 (31)	11 (23)	0.39
Renal insufficiency	12 (20)	5 (10)	0.28
Medication, *n* (%)			
Betablockers	22 (36)	24 (50)	0.17
ACE-inhibitors	20 (33)	19 (40)	0.54
ARB	17 (28)	11 (23)	0.66
CCB	19 (31)	13 (27)	0.67
Diuretics	23 (38)	20 (42)	0.69
Lipid-lowering medication	55 (90)	39 (81)	0.26
Aspirin	28 (46)	35 (73)	0.75
Clopidogrel	1 (1.5)	4 (8)	n.a
Aspirin + clopidogrel	4 (7)	3 (6)	n.a
Anticoagulants	2 (3)	2 (4)	n.a
Antiplatelets + anticoagulants	2(3)	4 (8)	n.a

Data are mean and standard error of mean for quantitative variables and number (percentages) for categorical variables. n.a: not applicable due to sample size. ABI: ankle-brachial arterial pressure index, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blockers, CCB: calcium channel blockers.

without revascularisation procedure. It is well known that a successful lower-limb revascularisation results in an improved perfusion of the treated leg and hence in an increase of ABI, which is not only a maker of limb perfusion but also linked to survival.[3,7] In contrast, there are few studies that evaluated effects of peripheral interventions on systemic markers of vascular function.[22]

To our knowledge, this is the first study that examined the effect of lower-limb revascularisation on AIx. Although our study does not give direct mechanistic insights, there

Table 2. Lesions characteristics ($n = 71$) of the revascularized patients ($n = 61$).

Lesion localisation, *n* (%)	
Iliac	17 (24)
Femoro-popliteal	54 (76)
Lesion type, *n* (%)	
Stenosis <5 cm length	38 (53)
Stenosis >5 cm length	17 (24)
Occlusion	16 (23)
Stenting, *n* (%)	
Iliac	11 (16)
Femoro-popliteal	15 (21)
Stented patients	22 (36)

Table 3. Pressure characteristics of study population at baseline.

	PTA ($n = 61$)	Control ($n = 48$)	p
Heart rate (bpm)	71.2 (1.3)	65.7 (1.1)	0.05
pSBP (mmHg)	146 (2.8)	153 (3.3)	0.07
pDBP (mmHg)	77.1 (1.4)	81.7 (1.5)	0.07
pMP (mmHg)	101.3 (2)	106.1 (1.8)	0.05
pPP (mmHg)	69 (2.1)	71.1 (2.9)	0.68
cSBP (mmHg)	130.8 (2.3)	134.8 (2.5)	0.16
cDBP (mmHg)	78.4 (1.5)	84.9 (2.3)	0.05
cPP (mmHg)	56.4 (1.9)	59.3 (2.8)	0.51

Data are mean and standard error of mean.bpm: Beats per minute, BP: blood pressure, p: peripheral, c: central, S: systolic, D: diastolic, MP: mean pressure, PP: pulse pressure.

are several potential explanations for that finding. Patients with successful angioplasty can increase pain-free walking distances, which, in turn, might increase physical activity.[23] It has been demonstrated that cardiovascular fitness is inversely related to arterial stiffness in healthy subjects and that lifestyle modifications such as taking up aerobic exercise is an efficacious therapeutic intervention to prevent and treat arterial stiffening.[24,25] Along the same lines, Brewer et al. showed that arterial stiffness is associated with walking distance in PAD patients by demonstrating that a higher AIx results in shorter distance.[26] We can therefore speculate that in patients undergoing angioplasty, the resulting reduction in AIx can be explained by improved functional capacity. Furthermore, repeated muscle ischaemia induces local inflammatory and oxidative stress responses, with free-radical formation, neutrophil activation and systemic vascular endothelial damage.[27,28] Successful revascularisation attenuates this type of ischaemia as well as the generation of reactive oxygen species[22] and thus increases the nitric oxide bioavailability, which plays an important role in arterial-wall compliance.[29–31] The present study did not assess physical activity or nitric oxide bioavailability, but we have previously found that flow-mediated dilation, which is directly dependent on nitric oxide, improved following successful lower-limb revascularisation.[22] Moreover a pharmacological intervention study using flavonoid supplementation provided evidence that

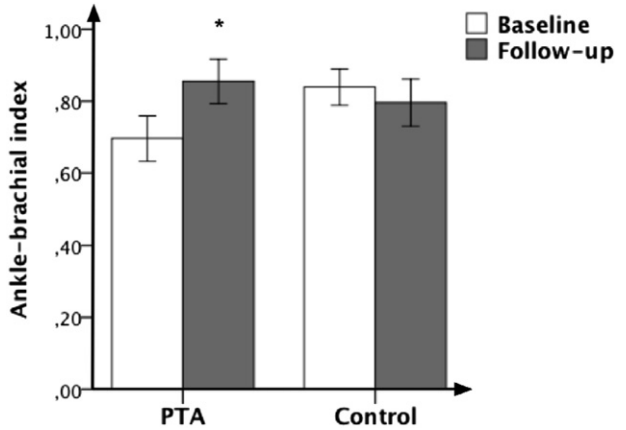

Figure 1. Ankle–brachial index in PTA group and control patients at baseline and at 3 months follow-up. *$p = 0.001$.

Table 4. Pressure characteristics of study population at 3-months follow-up.

	PTA ($n = 61$)	Control ($n = 48$)	p
Heart rate (bpm)	69.7 (1.3)	67.7 (1.8)	0.13
pSBP (mmHg)	141.9 (2.5)	145.7 (2.7)	0.26
pDBP (mmHg)	77.9 (1.4)	80.4 (1.4)	0.39
pMP (mmHg)	100.2 (1.7)	103 (1.7)	0.26
pPP (mmHg)	64.7 (2.2)	65.1 (2.5)	0.86
cSBP (mmHg)	130.8 (2.4)	134.8 (2.5)	0.16
cDBP (mmHg)	79 (1.4)	79.4 (2)	0.72
cPP (mmHg)	51.8 (2)	54.1 (2.4)	0.73

Data are mean and standard error of mean.bpm: Beats per minute, BP: blood pressure, p: peripheral, c: central; S: systolic, D: diastolic, MP: mean pressure, PP: pulse pressure.

there may be a link between a decrease in pulse-wave reflection and improved endothelial function.[32] Therefore; we may speculate that the observed improvement could be due to changes in the mediators of the endothelium such as nitric oxide. The attenuation of repeated muscle ischaemia and improved ambulation might synergistically act towards an improved nitric-oxide bioavailability that decreases peripheral-tissue resistance and thereby delays pulse-wave reflection, resulting in a lower AIx. In addition another important mechanism of pulse-wave reflection might play a role. The extent of arterial stiffness or obstructions and the number and pattern of arteries and arterioles of the distal run-off are important determinants of the timing and amplitude of the arterial-wave reflection.[33] Premature arterial-wave reflection may occur due to arterial obstructions. Therefore, removal of obstructions in peripheral arteries may delay wave reflection resulting in a decrease of AIx.

Despite the present findings and the fact that lower-extremity revascularisation ameliorates walking capacity, it remains unknown whether revascularisation has a beneficial effect on survival. However, Jaffery et al. have recently shown a trend towards lower 5-year mortality rates in PAD patients following lower-limb revascularisation when compared to PAD patients treated conservatively.[34] Data are limited so far and larger, randomised studies with clinical 'end' points are needed to answer that question.

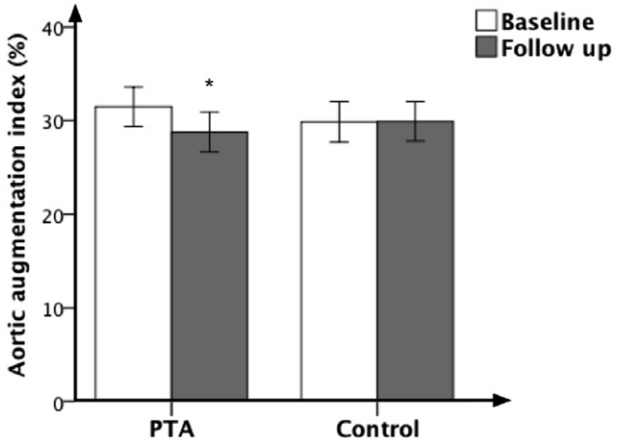

Figure 2. Augmentation index in PTA and control patients at baseline and at 3 months follow-up. *$p = 0.01$.

Limitation of the study

First, the present study is a controlled but non-randomised trial on the effect of lower-limb angioplasty on markers of arterial stiffness. Second, the ABI at baseline was significantly lower in the PTA group, indicating a more impaired lower-limb perfusion in that group. Nevertheless, this limitation does not reduce the significance of our findings, since both groups were followed up and only the PTA group exhibited beneficial changes of markers for arterial stiffness over this time. Third, patients in the conservatively treated group did not attend a supervised exercise programme, which might have similar effects on AIx as revascularisation. This should be further investigated, since physical activity has been shown to decrease cardiovascular morbidity and mortality.

CONCLUSION

Our study demonstrates for the first time that endovascular lower-extremity revascularisation significantly improves AIx, a surrogate marker of arterial stiffness.

CONFLICT OF INTEREST/FUNDING

No conflicts of interest. The study has been funded by the Swiss Heart Foundation and matching funds from the University Hospital of Zürich.

REFERENCES

1 Criqui MH. Peripheral arterial disease — epidemiological aspects. Vasc Med 2001;6:3—7.
2 Criqui MH, Denenberg JO, Bird CE, Fronek A, Klauber MR, Langer RD. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. Vasc Med 1996;1:65—71.
3 Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381—6.
4 Criqui MH, Ninomiya JK, Wingard DL, Ji M, Fronek A. Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. J Am Coll Cardiol 2008;52:1736—42.
5 Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. J Am Med Assoc 2008;300:197—208.
6 Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. J Am Med Assoc 2001;286:1317—24.
7 Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing;

TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol 2006;47:1239—312.
8 Vidula H, Tian L, Liu K, Criqui MH, Ferrucci L, Pearce WH, et al. Biomarkers of inflammation and thrombosis as predictors of near-term mortality in patients with peripheral arterial disease: a cohort study. Ann Intern Med 2008;148:85—93.
9 Gardner AW, Montgomery PS, Parker DE. Physical activity is a predictor of all-cause mortality in patients with intermittent claudication. J Vasc Surg 2008;47:117—22.
10 McDermott MM, Greenland P, Ferrucci L, Criqui MH, Liu K, Sharma L, et al. Lower extremity performance is associated with daily life physical activity in individuals with and without peripheral arterial disease. J Am Geriatr Soc 2002;50:247—55.
11 McDermott MM, Liu K, O'Brien E, Guralnik JM, Criqui MH, Martin GJ, et al. Measuring physical activity in peripheral arterial disease: a comparison of two physical activity questionnaires with an accelerometer. Angiology 2000;51:91—100.
12 Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, et al. Central blood pressure measurements and antihypertensive therapy: a consensus document. Hypertension 2007;50:154—60.
13 Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27:2588—605.
14 Laurent S, Boutouyrie P. Arterial stiffness: a new surrogate end point for cardiovascular disease? J Nephrol 2007;20(Suppl. 12): S45—50.
15 Prince CT, Secrest AM, Mackey RH, Arena VC, Kingsley LA, Orchard TJ. Pulse wave analysis and prevalent cardiovascular disease in type 1 diabetes. Atherosclerosis 2010;213:469—74.
16 Rabkin SW, Chan SH, Sweeney C. Ankle—brachial index as an indicator of arterial stiffness in patients without peripheral artery disease. Angiology 2012;63:150—4.
17 Khaleghi M, Kullo IJ. Aortic augmentation index is associated with the ankle-brachial index: a community-based study. Atherosclerosis 2007;195:248—53.
18 Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. Circulation 1997;95:1827—36.
19 Gallagher D, Adji A, O'Rourke MF. Validation of the transfer function technique for generating central from peripheral upper limb pressure waveform. Am J Hypertens 2004;17:1059—67.
20 Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension 2001;38:932—7.
21 Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, et al. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 1998;16:2079—84.
22 Husmann M, Dorffler-Melly J, Kalka C, Diehm N, Baumgartner I, Silvestro A. Successful lower extremity angioplasty improves brachial artery flow-mediated dilation in patients with peripheral arterial disease. J Vasc Surg 2008;48:1211—6.
23 Nylaende M, Abdelnoor M, Stranden E, Morken B, Sandbaek G, Risum Ø, et al. The Oslo balloon angioplasty versus conservative treatment study (OBACT) — the 2-years results of a single centre, prospective, randomised study in patients with intermittent claudication. Eur J Vasc Endovasc Surg 2007;33:3—12.
24 Kingwell BA. Large artery stiffness: implications for exercise capacity and cardiovascular risk. Clin Exp Pharmacol Physiol 2002;29:214—7.
25 Tanaka H, Safar ME. Influence of lifestyle modification on arterial stiffness and wave reflections. Am J Hypertens 2005;18: 137—44.
26 Brewer LC, Chai HS, Bailey KR, Kullo IJ. Measures of arterial stiffness and wave reflection are associated with walking distance in patients with peripheral arterial disease. Atherosclerosis 2007;191:384—90.
27 Turton EPL, Spark JI, Mercer KG, Berridge DC, Kent PJ, Kester RC, et al. Exercise-induced neutrophil activation in claudicants: a physiological or pathological response to exhaustive exercise? Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg 1998;16:192—6.
28 Welbourn CR, Goldman G, Paterson IS, Valeri CR, Shepro D, Hechtman HB. Pathophysiology of ischaemia reperfusion injury: central role of the neutrophil. Br J Surg 1991;78:651—5.
29 Wilkinson I, MacCallum H, Cockcroft J, Webb D. Inhibition of basal nitric oxide synthesis increases aortic augmentation index and pulse wave velocity in vivo. Br J Clin Pharmacol 2002;53: 189—92.
30 Kinlay S, Creager MA, Fukumoto M, Hikita H, Fang JC, Selwyn AP, et al. Endothelium-derived nitric oxide regulates arterial elasticity in human arteries in vivo. Hypertension 2001;38:1049—53.
31 Schmitt M, Avolio A, Qasem A, McEniery CM, Butlin M, Wilkinson IB, et al. Basal NO locally modulates human iliac artery function in vivo. Hypertension 2005;46:227—31.
32 Teede HJ, McGrath BP, DeSilva L, Cehun M, Fassoulakis A, Nestel PJ. Isoflavones reduce arterial stiffness: a placebo-controlled study in men and postmenopausal women. Arterioscler Thromb Vasc Biol 2003;23:1066—71.
33 Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. Circulation 2003;107:2864—9.
34 Jaffery Z, Greenbaum AB, Siddiqui MF, Mahendraker N, Gupta V, Mokkala V, et al. Predictors of mortality in patients with lower extremity peripheral arterial disease: 5-year follow-up. J Interv Cardiol 2009;22:564—70.